THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 25

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RICHARD A. GREENE and GERALD J. LITT

Appeal No. 95-4404
Application 07/913,121[1]

ON BRIEF

Before WILLIAM F. SMITH, ELLIS and LORIN, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

[1] Application for patent filed July 14, 1992. According to appellants, the application is a continuation-in-part of Application 07/821,512, filed January 15, 1992, now abandoned.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1-19, all the claims pending in the application. Independent claims 1, 8 and 14 are illustrative of the subject matter on appeal and read as follows:

1. A method for detecting reverse transcriptase in a sample suspected of containing reverse transcriptase comprising the steps of:

(A) incubating a synthetic heteropolymeric RNA template molecule containing 40-500 nucleotides with an oligonucleotide primer complementary to a portion of said RNA molecule and of sufficient length to form a stable template-primer complex:

(B) contacting the complex formed in step (A) with a sample suspected of containing reverse transcriptase under conditions leading to the production of a cDNA strand complementary to the template RNA and hybridized thereto if reverse transcriptase was present;

(C) degrading the RNA template from the RNA-cDNA complex formed in step (B) resulting in single stranded cDNA;

(D) hybridizing said cDNA with a chemically modified oligonucleotide probe or probes to permit capture and/or detection of the cDNA-probe complex formed;

(E) separating the cDNA-probe complex formed in step (D) from unreacted probe, wherein steps (D) and (E) may be carried out sequentially or simultaneously; and

(F) detecting the presence of reverse transcriptase by detecting a label in a labeled cDNA complex, wherein said label is introduced into said complex from labeled oligonucleotide primer, labeled oligonucleotide probe or a labeled third oligonucleotide when the primer is unmodified.

8. A method for detecting and/or quantitating drug resistance of reverse transcriptase in a sample which comprises:

(A) incubating a synthetic heteropolymeric RNA template molecule containing

40-500 nucleotides with an oligonucleotide primer complementary to a portion of said RNA molecule and of sufficient length to form a stable template-primer complex;

(B) contacting the complex formed in step (A) with a sample containing reverse transcriptase and at least one drug known to have reverse transcriptase inhibitory activity under conditions leading to the production of a cDNA strand complementary to the template RNA and hybridized thereto if the reverse transcriptase was not inhibited by the drug;

(C) degrading the RNA template from the RNA-cDNA complex if formed in step (B) resulting in single stranded cDNA;

(D) hybridizing said cDNA if formed with a chemically modified oligonucleotide probe or probes to permit capture and/or detection of the cDNA-probe complex formed;

14. A method for detecting and/or quantitating the reverse transcriptase inhibitory activity of a compound which comprises:

(A) incubating a synthetic heteropolymeric RNA template molecule containing 40-500 nucleotides with an oligonucleotide primer complementary to a portion of said RNA molecule and of sufficient length to form a stable template-primer complex;

(B) contacting the complex formed in step (A) with an appropriate reverse transcriptase standard and at least one compound suspected to be a reverse transcriptase inhibitor under conditions lead to the product of a cDNA strand complementary to the template RNA and hybridized thereto if the reverse transcriptase was not inhibited by the drug;

(C) degrading the RNA template from the RNA-cDNA complex if formed in the presence of the compound in step (B) resulting in single stranded cDNA;

(D) hybridizing said cDNA if formed in the presence of the compound with a chemically modified oligonucleotide probe or probes to permit capture and/or detection of the cDNA-probe complex formed;

(E) separating the cDNA-probe complex if formed in the presence of the compound in step (D) from unreacted probe, wherein steps (D) and (E) can be carried out sequentially or simultaneously; and

(F) detecting and/or quantitating a label in a labeled cDNA complex, wherein said label is introduced into said complex from labeled oligonucleotide primer, labeled oligonucleotide probe or a labeled third oligonucleotide when the primer is unmodified, and further wherein the amount of label is a measure of the resistance of the reverse transcriptase to the drug or drugs evaluated at the concentration tested.

The references relied upon by the examiner are:

Mizoguichi (European Patent Document)	0,392,459	Oct. 17, 1990
Holmes	WO 90/06044	Jun. 14, 1990

Urdea et al, (Urdea), "A comparison of non-radioisotopic hybridization assay methods using fluorescent, chemiluminescent and enzyme labeled synthetic oligodeoxyribonucleotide probes", Nucleic Acids Research, vol. 16, no. 11, pp. 4937-4956 (1988).

Goff, "Retroviral Reverse Transcriptase: Synthesis, Structure, and Function", Journal of Acquired Immune Deficiency Syndromes, vol. 3, pp. 817-831 (1990).

Laquel et al., (Laquel), "Wheat embryo DNA polymerase A reverse transcribes natural and synthetic RNA templates. Biochemical characterization and comparison with animal DNA polymerase p and retroviral reverse transcriptase", Biochem. Biophys. Acta, vol. 1048, pp. 139-148 (1990).

Mogensen et al. (Mogensen), "Nonradioactive, Sequence-Specific Detection of RNA in Situ by Primed in Situ Labeling (PRINS)", Experimental Cell Research, vol. 196, pp. 92-98 (1991).

Konig et al., (Konig), "A Highly Sensitive Non-Radioactive Microassay For HIV-1 Reverse Transcriptase", Journal of Cell Cellular Biochemistry, suppl. 16E, pg. Q222 (March 27,

1992).

A patent discussed by the merits panel is:

Eberle et al. (Eberle)	5,413,906	May 9, 1995

The claims stand rejected as follows:

(1) Claims 1 through 7 and 14 through 19 under 35 U.S.C. § 103 as unpatentable over Mizoguchi in view of Mogensen, Holmes and Urdea.

(2) Claims 1 through 7 and 14 through 19 under 35 U.S.C. § 103 as unpatentable over Mizoguchi in view of Laquel, Holmes and Urdea.

(3) Claims 8 through 13 under 35 U.S.C. § 103 as unpatentable over Mizoguchi in view of Mogensen, Holmes and Urdea, and further in view of Goff.

(4) Claims 8 through 13 under 35 U.S.C. § 103 as unpatentable over Mizoguchi in view of Laquel, Holmes and Urdea, and further in view of Goff.

(5) Claims 14 through 19 under 35 U.S.C. § 103 as unpatentable over Konig in view of Urdea and Holmes.

(6) Claims 8 through 13 under 35 U.S.C. § 103 as unpatentable over Konig in view of Urdea and Holmes, and further in view of Goff.

We reverse each rejection based on Mizoguchi and affirm those based on Konig. In addition, we raise an issue for the examiner to consider upon return of the application.

BACKGROUND

Retrovirus particles contain active reverse transcriptase which is essential for replication of the retroviral single stranded RNA genome. Reverse transcriptase is a multifunctional enzyme with three distinct enzymatic activities: RNA-dependent DNA polymerase activity, RNase H activity, and DNA-dependent DNA polymerase activity. During replication in a host cell, RNA-dependent DNA polymerase activity generates a DNA strand (cDNA) complementary to the viral RNA and the original viral RNA strand is degraded by Rnase H activity. Next, a second DNA strand, complementary to the cDNA, is generated by DNA-dependent DNA polymerase activity. The resultant double stranded DNA is integrated into the host genome, and the cellular machinery of the host is commandeered to replicate more retrovirus particles. Retroviruses can be indirectly detected through detection of reverse transcriptase RNA-dependent DNA polymerase activity. See the Specification, pages 1 through 3.

DISCUSSION

The claimed invention is directed to a method for detecting reverse transcriptase in a sample through the ability of the reverse transcriptase to synthesize cDNA. Claims 1-7 comprise: incubating a synthetic heteropolymeric RNA template with a complementary oligonucleotide primer to form a template-primer complex; incubating the template-primer complex with the sample to form a cDNA-RNA duplex if reverse transcriptase is present;

degrading the RNA from the duplex to form free cDNA; hybridizing the cDNA with a chemically modified probe or probes to form cDNA-probe(s) complex capable of being captured and/or detected; separating the cDNA-probe(s) complex from unreacted probe(s); and detecting the presence of reverse transcriptase by detecting the cDNA-probe(s) complex. Claims 8-13 are directed to an alternative embodiment wherein drug resistant forms of reverse transcriptases are detected by performing the method in the presence of a known reverse transcriptase inhibitor. Claims 14-19 are directed to yet another embodiment wherein reverse transcriptase inhibitors are identified by performing the method in the presence of candidate compounds.

Mizoguchi

The examiner has rejected all of the claims as obvious over Mizoguchi in combination with Mogensen, Holmes, Urdea and Goff, and in the alternative, as obvious over Mizoguchi in combination with Laquel, Holmes, Urdea and Goff.

Mizoguchi discloses a method of detecting reverse transcriptase in a biological sample wherein a synthetic adenine ribopolynucleotide RNA (poly A) template is incubated with an oligodeoxythyminenucleotide (oligo dT) primer to form a template-primer complex; the template-primer complex is incubated with the biological sample and labeled nucleotide substrate, allowing synthesis of a labeled cDNA-RNA duplex if reverse transcriptase is present in the sample; unreacted template and substrate are separated

from the cDNA-RNA duplex; and the cDNA-RNA duplex is detected through the label incorporated during synthesis of the cDNA. Foremost among the many differences between Mizoguchi and the claimed invention is Mizoguchi's use of a synthetic poly A template and an oligo dT primer, rather than a synthetic heteropolymeric RNA template and complementary heteropolymeric primer.

Mogensen is relied upon as evidence that one of ordinary skill in the art would have found it obvious to substitute a heteropolymeric template and complementary primer for Mizoguchi's poly A template and oligo dT primer. Mogensen discloses a method for detecting specific RNA transcripts based upon sequence-dependent annealing of specific oligonucleotide primers to intracellular RNA followed by reverse transcriptase catalyzed chain elongation with labeled nucleotides. The method detects intracellular RNA transcripts in situ or extracted from cells and so does not involve a synthetic RNA template, but the oligonucleotide primers are synthetic DNA heteropolymers as they are designed to be complementary to the intracellular RNA transcripts. Holmes, Urdea and Goff are relied upon as evidence that one of ordinary skill in the art would have found it obvious to modify all of the other steps of Mizoguchi in the manner required to arrive at the claimed subject matter.

We view the examiner's proposed combination of Mizoguchi and Mogensen as the dispositive issue here. The examiner believes that one of ordinary skill in the art would

have found it obvious to combine Mizoguchi and Mogensen, substituting Mogensen's specific heteropolymeric primer (along with a complementary synthetic heteropolymeric template not disclosed by Mogensen) for Mizoguchi's poly A template and oligo dT primer. The reason, suggestion or motivation to combine the references[2] in this manner according to the examiner is that "the reaction could have been performed using RT samples containing both non-specific templates (i.e. poly A mRNA) and specific templates and only the synthetic heteropolymeric template would be utilized in the reverse transcriptase reaction . . . provid[ing] the advantage of increasing the specificity of the reverse transcriptase reaction thereby providing more accurate and reproducible results regarding the amount of RT present in a sample" (see the Answer, pages 5 and 6); and because "the ordinary artisan would have recognized that the 'specific template' taught by Mizoguchi is inclusive of both heteropolymeric and homopolymeric templates" (See the Answer, page 14).

We do not agree. As appellants point out, Mizoguchi is narrowly focused on substituting biotin-dUTP for a radiolabel in an otherwise conventional assay for reverse transcriptase. (See the Brief, pages 10 and 11). We do not view Mizoguchi as a general

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[2] As stated in Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996) (citation omitted), "It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references."

teaching reference, especially with respect to the "specific template" as all the templates disclosed in the reference are poly A templates (varying only by the length of the homopolymer). While one would recognize from Mogensen that heteropolymeric template primer pairs could be elongated by reverse transcriptase, we agree with appellants that this fact alone does not provide the needed reason, suggestion or motivation to disassemble Mizoguchi and reassemble it using a heteropolymeric template-primer pair instead of Mizoguchi's poly A template-oligo dT primer pair.

Laquel is relied upon as an alternative to Mogensen, again to provide evidence that it would have been obvious to one of ordinary skill in the art to substitute a heteropolymeric template and complementary primer for Mizoguchi's poly A template and oligo dT primer. Laquel discloses the purification and characterization of a wheat embryo DNA polymerase, comparing its properties with those of animal DNA polymerase gamma and a reverse transcriptase. Laquel teaches that reverse transcriptase is able to synthesize cDNA from a synthetic poly A template and from a natural RNA template, but animal polymerase gamma is unable to use the natural RNA template. Holmes, Urdea and Goff are relied upon to provide evidence that it would have been obvious to one of ordinary skill in the art to modify all of the other steps of Mizoguchi in the manner needed to arrive at the claimed subject matter.

In our view, the dispositive issue here is the examiner's proposed combination of

Mizoguchi and Laquel. The examiner believes that one of ordinary skill in the art would have found it obvious to substitute a heteropolymeric template and complementary primer for Mizoguchi's poly A template and oligo dT primer in Mizoguchi's method to avoid interference from animal polymerase gamma.

We do not agree. As before, we do not consider Mizoguchi to be a general teaching reference; instead we view Mizoguchi as narrowly focused on substituting a non-radioactive label for a radioactive one in an otherwise conventional assay for reverse transcriptase. We agree with appellants that one of ordinary skill in the art would not have found Laquel's teachings to provide suffiicient reason, suggestion or motivation to disassemble Mizoguchi's assay and reassemble it by replacing the poly A template-oligo dT primer pair with a heteropolymeric template-primer pair.

Taking a step back, we see no reason, other than hindsight based upon appellants' disclosure, to modify Mizoguchi's method to arrive at the claimed invention. The rejections based upon Mizoguchi in combination with Mogensen, and Mizoguchi in combination with Laquel are reversed.

Konig

The examiner has rejected claims 14-19 as obvious over Konig in combination with Urdea and Holmes, and claims 8-13 as obvious over Konig in combination with Urdea, Holmes and Goff. The publication date of Konig falls between the filing date of the present

application and parent application serial number 07/821,512. Therefore, our first consideration is whether claims 8-19 are entitled to the benefit of the earlier filing date under the provisions of 35 U.S.C. § 120. As required by § 120, the claims in this application must be described in the parent application in the manner provided by 35 U.S.C. § 112, first paragraph. For the purposes of deciding this appeal, we will focus on whether the rejected claims enjoy written description in the parent application. In so doing, we note that an issue arising under the written description requirement of 35 U.S.C. § 112, first paragraph, is a question of fact. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991).

The present claims are directed to methods "for detecting and/or quantitating drug resistance of reverse transcriptase in a sample" and "for detecting and/or quantitating the reverse transcriptase inhibitory activity of a compound" and include several limitations (i.e., steps) related to these objectives. The parent application discloses an assay for detecting reverse transcriptase but makes no mention of these specific objectives or limitations. Appellants point to the "BACKGROUND OF THE INVENTION" in the parent application wherein it is stated that "[d]etection of RT can be very important because this enzyme is a logical target for anti-viral therapy and, therefore, anti-viral drug screening can be carried out by RT detection" and argue that the claims "merely [make] explicit that which was clearly inherent in the specification." See Brief, page 17.

While it is well settled that claimed subject matter need not be supported by an explicit, word for word recitation, something more than a suggestion is needed to satisfy the requirement for an adequate written description. As set forth in Lockwood v. American Airlines Inc., 107 F.3d 1565, 1571-1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997):

> It is the disclosures of the applications that count. Entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. It extends only to that which is disclosed. While the meaning of terms, phrases, or diagrams in a disclosure is to be explained or interpreted from the vantage point of one skilled in the art, all the limitations must appear in the specification. The question is not whether a claimed invention is an obvious variant of that which is disclosed in the specification. Rather, a prior application itself must describe an invention, and do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought. . . [A]ll that is necessary to satisfy the description requirement is to show that one is "in possession" of the invention . . . One shows that one is "in possession" of the invention by describing the invention, with all its claimed limitations, not that which makes it obvious. . . Although the exact terms need not be used in haec verba, . . . the specification must contain an equivalent description of the claimed subject matter. (Citations omitted).
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> . . .
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> It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose. Each application in the chain must describe the claimed features.

The parent application makes only a passing reference to reverse transcriptase detection and anti-viral drug screening in the "BACKGROUND OF THE INVENTION."

There is no further mention of screening, or what that might entail, in the "STATEMENT OF THE INVENTION" or anywhere else in the application. Certainly, there is no disclosure of the specific steps recited in the present claims, nor is there any mention of drug resistant reverse transcriptases. We are in agreement with the examiner that the present claims do not enjoy written description in the parent application, and, therefore, are not entitled to the earlier filing date of the parent under 35 U.S.C. § 120.

Having determined that Konig is available as prior art, we turn to the rejections of claims 8-19 as obvious over Konig in combination with Urdea, Holmes and Goff.

Konig discloses a method for identifying inhibitors of reverse transcriptase. The method comprises: hybridizing a heteropolymeric HIV-1 RNA template and a complementary primer; incubating the template-primer pair with reverse transcriptase, biotin- and digoxygenin-labeled substrate molecules and a candidate inhibitor. Any cDNA synthesized is captured on a streptavidin-coated solid support and detected by peroxidase-labeled anti-digoxygenin antibody, so Konig does not disclose hydrolysis of the RNA template or detection of the cDNA using capture and/or labeled probes in a sandwich hybridization assay. Urdea and Holmes are cited to show that it is conventional to hydrolyze RNA in an RNA cDNA duplex with subsequent detection of the cDNA by sandwich hybridization. With respect to claims 8-13, Konig further differs from the claimed invention in not using the assay to detect drug resistant forms of reverse transcriptase.

Goff teaches that drug-resistant forms of reverse transcriptase are a serious problem in the treatment of AIDS patients, and discloses identification and isolation of drug-resistant variants.

The examiner's position is that it would have been obvious for one of ordinary skill in the art to have modified Konig's method by substituting the conventional, alternative capture and detection methods disclosed by Urdea and Holmes for Konig's capture and detection method for a number of reasons set forth on pages 22 through 24 of the Examiner's Answer. Additionally, the examiner believes that it would have been obvious to modify Konig's method of identifying reverse transcriptase inhibitors to identify drug-resistant forms of reverse transcriptase instead, by performing the assay in the presence of a known inhibitor.

Having considered the examiner's position, we find ourselves in agreement with the examiner that the prior art relied upon would have rendered the claimed invention obvious to one of ordinary skill in the art. Appellants have not presented any arguments against the prima facie case except to say that "[t]here is no teaching or suggestion for identifying drug resistant forms of RT as is recited in claims 8-13." (See the Brief, page 19) . Again, we agree with the examiner that Goff provides ample reason, suggestion or motivation for modifying Konig's assay to detect drug resistant forms of reverse transcriptase, and, therefore, it would have been well within the ability of one of ordinary skill in the art to have

done so.

The examiner's rejections of claims 14-19 as obvious over Konig in combination with Urdea and Holmes, and of claims 8-13 as obvious over Konig in combination with Urdea, Holmes and Goff are affirmed.

OTHER ISSUES

Claims 1-7 are now free of rejection. However, the merits panel has become aware of the issuance of U.S. Patent No. 5,413,906 to Eberle; this patent claims priority to a PCT with a publication date of March 19, 1992. Upon return of this application, the examiner should review Eberle and determine whether the claims of the patent and claims 1-7 of this application are directed to the same patentable invention. If so, it appears that the question of interference arises.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

WILLIAM F. SMITH)

Administrative Patent Judge	)	
	)	
	)	
	)	
JOAN ELLIS	)	BOARD OF PATENT
Administrative Patent Judge	)	APPEALS AND
	)	INTERFERENCES
	)	
	)	
HUBERT C. LORIN	)	
Administrative Patent Judge	)	

Ronald W. Citkowski
Gifford, Krass, Groh, Sprinkle, Patmore,
Anderson & Citkowski, P.C.
280 N. Old Woodward, Ste. 400
Birmingham, MI 48009-5364

WFS/ki